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Effects of unilateral repetitive transcranial magnetic stimulation of the motor cortex on chronic widespread pain in fibromyalgia

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Non-invasive unilateral repetitive transcranial magnetic stimulation (rTMS) of the motor cortex induces analgesic effects in focal chronic pain syndromes, probably by modifying central pain modulatory systems. Neuroimaging studies have shown bilateral activation of a large number of structures, including some of those involved in pain processing, suggesting that such stimulation may induce generalized analgesic effects. The goal of this study was to assess the effects of unilateral rTMS of the motor cortex on chronic widespread pain in patients with fibromyalgia. Thirty patients with fibromyalgia syndrome (age: 52.6 ± 7.9) were randomly assigned, in a double-blind fashion, to two groups, one receiving active rTMS ($n = 15$) and the other sham stimulation ($n = 15$), applied to the left primary motor cortex in 10 daily sessions. The primary outcome measure was self-reported average pain intensity over the last 24 h, measured at baseline, daily during the stimulation period and then 15, 30 and 60 days after the first stimulation. Other outcome measures included: sensory and affective pain scores for the McGill pain Questionnaire, quality of life (assessed with the pain interference items of the Brief Pain Inventory and the Fibromyalgia Impact Questionnaire), mood and anxiety (assessed with the Hamilton Depression Rating Scale, the Beck Depression Inventory and the Hospital Anxiety and Depression Scale). We also assessed the effects of rTMS on the pressure pain threshold at tender points ipsi- and contralateral to stimulation. Follow-up data were obtained for all the patients on days 15 and 30 and for 26 patients (13 in each treatment group) on day 60. Active rTMS significantly reduced pain and improved several aspects of quality of life (including fatigue, morning tiredness, general activity, walking and sleep) for up to 2 weeks after treatment had ended. The analgesic effects were observed from the fifth stimulation onwards and were not related to changes in mood or anxiety. The effects of rTMS were more long-lasting for affective than for sensory pain, suggesting differential effects on brain structures involved in pain perception. Only few minor and transient side effects were reported during the stimulation period. Our data indicate that unilateral rTMS of the motor cortex induces a long-lasting decrease in chronic widespread pain and may therefore constitute an effective alternative analgesic treatment for fibromyalgia.

Keywords: chronic pain; muscle pain; pain modulation; transcranial magnetic stimulation

Abbreviations: BPI = Brief Pain Inventory; rTMS = Repetitive transcranial magnetic stimulation; PPT = Pressure pain thresholds

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Introduction

Repetitive transcranial magnetic stimulation (rTMS) is a safe non-invasive technique for stimulating the cerebral cortex (Kobayashi and Pascual-Leone, 2003). In addition to its uses in cognitive neuroscience, the clinical applications of rTMS have rapidly expanded over the last few years.

This technique was initially proposed and has been most thoroughly studied for the treatment of depression (Pascual-Leone *et al.*, 1996; Martin *et al.*, 2003; Benadhira *et al.*, 2005; Januel *et al.*, 2006). However, rTMS may also be useful for the treatment of other psychiatric and neurological conditions, including schizophrenia, Parkinson's disease and tinnitus (Fregni *et al.*, 2005; Londero *et al.*, 2006; Saba *et al.*, 2006). Furthermore, recent studies have shown that rTMS applied to the motor cortex can induce analgesic effects in patients with focal chronic pain syndromes (Migita *et al.*, 1995; Lefaucheur *et al.*, 2001, 2004; Khedr *et al.*, 2005; Fregni *et al.*, 2007). Several neuroimaging studies have shown that rTMS of the motor cortex induces changes not only in local brain activity, but also bilaterally in a number of remote cortical and subcortical areas, including some of those involved in pain processing (Bohning *et al.*, 2000; Bestmann *et al.*, 2004, 2005; Rounis *et al.*, 2005). Thus, the analgesic effects of rTMS, which may result largely from modifications to central pain modulatory systems (Lefaucheur, 2006), may be generalized.

Fibromyalgia is a chronic pain disorder characterized by widespread pain and muscle tenderness, often accompanied by sleep disorders, fatigue and depression (Mease, 2005). It has an estimated prevalence of 1–3% in the general population, and affects predominantly women (Wolfe *et al.*, 1995; Mease, 2005). The aetiology and pathogenesis of fibromyalgia are poorly understood (Wolfe, 1997), but these patients present with alterations of central pain processing which may primarily affect pain modulatory systems (Kosek and Hansson, 1997; Lautenbacher and Rollman, 1997; Staud *et al.*, 2003*a*, *b*, 2005; Price and Straud, 2005). Functional neuroimaging studies have confirmed that fibromyalgia is associated with changes in the activity of brain structures involved in pain processing (Mountz *et al.*, 1995; Gracely *et al.*, 2002, 2004; Giesecke *et al.*, 2005).

We therefore hypothesized that rTMS of the motor cortex might reduce chronic widespread pain in patients with fibromyalgia. This hypothesis is supported by recent reports that non-invasive direct transcranial current stimulation of the motor cortex has analgesic effect in fibromyalgia patients (Fregni *et al.*, 2006).

We report here the results of a randomized, double-blind, sham-controlled parallel group study analysing the analgesic effects of repeated daily sessions of unilateral rTMS in patients with widespread pain due to fibromyalgia. We also evaluated the effects of rTMS on quality of life, mood, anxiety and pain threshold at tender points as secondary outcomes.

Methods

This study was conducted at Ambroise Paré Hospital, Boulogne–Billancourt and Ville–Evrard Hospital, Saint-Denis, from April 2004 to July 2005. The protocol was approved by local ethics committee and all patients provided written informed consent before inclusion in the study.

Patients

Right-handed patients of at least 18 years of age, naive for rTMS, who met the ACR criteria for fibromyalgia (Wolfe *et al.*, 1990) and had suffered persistent pain for more than 6 months, were eligible for the study. Patients were required to have a score of at least 4 out of 10 on the mean daily pain intensity numerical scale of the Brief Pain Inventory (Cleeland and Ryan, 1994) during the baseline week preceding randomization and to have completed at least 4 pain diaries out of 7. At screening, all patients underwent physical examination by a pain specialist, followed by laboratory tests if necessary and a psychiatric interview with a psychiatrist. Patients were excluded if evidence was found of inflammatory rheumatic disease, auto immune disease or other painful disorders that might confound the assessment of fibromyalgia pain, current primary psychiatric conditions—including major depression or major personality disorders according to DSM-IV criteria—or a history of substance abuse. All women of child-bearing age included in this study had negative pregnancy tests at inclusion and were using contraception. Patients with contra indications for transcranial magnetic stimulation—a history of seizures, brain trauma, brain surgery or intracranial hypertension, a pace maker or other metallic implants—were also excluded. Concomitant medication for pain and sleep disorders was authorized, provided the dose administered had been stable for at least 1 month before enrolment and remained stable throughout the study. Patients were instructed to maintain their normal daily routines and not to alter their pattern of exercise throughout the study.

Experimental design

During a 1-week baseline observation period, patients were asked to report each morning their mean pain intensity in a diary over the last 24 h. At the end of the baseline phase, patients who met all inclusion criteria were randomly assigned, according to a computer-generated list, to two groups—one given active and the other sham stimulation—with equal numbers in each group. The treatment protocol consisted of one session per day for five consecutive days followed by 2 days without treatment and then another five consecutive days of treatment (i.e. a total of 10 sessions per patient over two consecutive weeks). Both patients and investigators were blind to treatment group. Transcranial stimulation was applied by an independent investigator not involved in the selection or assessment of the patients. Patients were asked to report daily their mean pain intensity during the stimulation periods (i.e. from day 1 to 14) and follow-up visits were scheduled for assessments at day 15, 30 ± 2 and 60 ± 4 after the start of the treatment (i.e. 3, 17 and 39 days after the last stimulation).

Transcranial magnetic stimulation

Magnetic stimulation was applied using a Super-Rapid Magstim Stimulator (Magstim Co., Whitland, UK) with a figure-of-eight-shaped coil. The rTMS parameters were similar to those used in the previous studies reporting clinical effects of rTMS in chronic focal pain (Lefaucheur *et al.*, 2004; Fregni *et al.*, 2007). Each treatment session consisted of 25 series of eight-second pulses, with 52 s interval between series, at

a stimulation frequency of 10 Hz and 80% resting motor threshold intensity, giving a total of 2000 pulses per session. The resting motor threshold (MT) was determined before each session, using a single-pulse stimulation over the left primary motor cortex. Motor evoked potentials were recorded from the thenar muscles of the right hand, using a standard EMG machine and surface electrodes. The MT was defined as the lowest intensity required to elicit a motor evoked potential in 50% of successive trials. During stimulation the coil was oriented at a tangent to the scalp in the anterior–posterior direction and fixed to an arm that could be adjusted in three dimensions. Sham stimulation was carried out with the 'Magstim placebo coil system', which physically resembles the active coil and makes similar sounds.

Outcome measures

The primary outcome measure was self-reported average pain intensity over the last 24 h using the 11-point numerical scale (0: no pain; 10: maximal pain imaginable) of the Brief Pain Inventory (Cleeland and Ryan, 1994). Average pain intensity was reported each morning by the patient in a diary for 1 week before treatment (baseline period), during treatment and until the first follow-up visit (i.e. from day 1 to day 14) to make it possible to determine the onset of treatment effects, then was assessed at each follow-up visit on days 15, 30 ± 2 and 60 ± 4.

Secondary outcome measures were assessed at baseline (on day 1 before the first stimulation), then at each follow-up visit.

The Brief Pain Inventory items for pain interference (from 0: does not interfere, to 10: complete interference) were used to measure the impact of pain on general activity, mood, walking ability, normal work, relations with other people, sleep and enjoyment of life (Cleeland and Ryan, 1994).

The French version (Boureau *et al.*, 1992) of the McGill Pain Questionnaire (Melzack, 1975) was used to measure the sensory and affective dimensions of pain.

The percentage subjective pain relief from the treatment over the past week (from 0%: no pain relief to 100%: maximal pain relief) was recorded at each follow-up visit.

The effects of the treatment on the health domains most affected by fibromyalgia were assessed with the French version (Perrot *et al.*, 2003) of the Fibromyalgia Impact Questionnaire (FIQ) (Burckhardt *et al.*, 1991). Both the FIQ total score, with ranges from 0 (no impact) to 100 (maximum impact) and the FIQ subscales (from 0 to 10) for fatigue, morning tiredness and stiffness were included in the analysis.

The manual tender point survey (Okifuji *et al.*, 1997) was used to calculate the number of tender points.

Pressure pain thresholds (PPT) were systematically measured at four tender points on both sides (trapezius muscle, lateral epicondyle, trochanter, knee), using a calibrated pressure algometer (Somedic, Sweden) with a probe area of 1 cm^2 and a rate of pressure of 50–60 kPa/s. PPT (expressed in kPa) was determined by the method of limits, by applying series of increasing strength until the pain threshold identified by the patients (Kosek *et al.*, 1996; Kosek and Hansson, 1997).

Mood and anxiety were assessed with (i) the 17-item Hamilton Depression Rating Scale; (ii) the self-administered 13-item short form of the Beck Depression Inventory (Beck *et al.*, 1974) and (iii) the self-administered 14-item Hospital Anxiety and Depression Scale (Zigmond and Snaith, 1983).

Table 1 Patients' Characteristics and Baseline Values

	Active rTMS group (n = 15)	Sham-stimulation group (n = 15)
Characteristics (mean ± *SD*)		
Age (years)	52.6 ± 7.9	55.3 ± 8.9
Pain duration (years)	8.1 ± 7.9	10.9 ± 8.6
BPI average intensity (0–10)	6.8 ± 1.3	6.5 ± 1.2
Concomitant treatment (% of patients)		
Weak analgesics (n)	10	9
Opioid analgesics (n)	1	1
Antidepressants (n)	8	10
NSAIDS (n)	3	3
Benzodiazepines (n)	5	6

BPI = brief pain inventory; NSAIDs = non-steroidal anti-inflammatory.

The safety of rTMS was assessed by monitoring the occurrence of adverse effects during treatment and analysing the treatment discontinuation pattern for all patients randomized in the two treatment groups.

Statistical analysis

Changes between the baseline and the endpoint after treatment in the Brief Pain Inventory average pain severity score and all secondary efficacy variables (BPI-Interference scores, number of tender points, scores for the FIQ, HAD, BDI and HDRS, pressure pain thresholds) were compared between the active and sham stimulation groups. A repeated measures analysis of variance (ANOVA) was carried out in which the dependent variable was one of the outcome measures and the factors were treatment group (active or sham rTMS) and time (baseline, D15, D30 and D60). Bonferroni correction was used for *post hoc* comparisons. Pearson's correlation coefficient was used to analyse the correlations between pairs of variables. Fisher's exact test was used to compare categorical variables. All randomized patients with a baseline and at least one post-baseline visit with efficacy data were included in the efficacy analyses (intent to treat analysis). In all cases, P-values <0.05 were considered significant.

Results

We screened 38 patients and the 30 patients (29 women, 1 man) meeting the inclusion criteria were randomly assigned to the active rTMS ($n = 15$) or sham stimulation ($n = 15$) groups. Sociodemographic variables, clinical characteristics and concomitant analgesic treatments did not differ significantly between the two groups (Table 1). All the patients received the full course of treatment and were assessed on D15 and D30. Four patients (two in each treatment group) withdrew from the trial between days 30 and 60.

Effects of rTMS on pain

Pain intensity was similar in the two groups at baseline and rTMS had a significant effect on average pain intensity score between baseline and day 15 ($P < 0.05$) for comparison with sham stimulation, with an effect size of 1.10 at 15

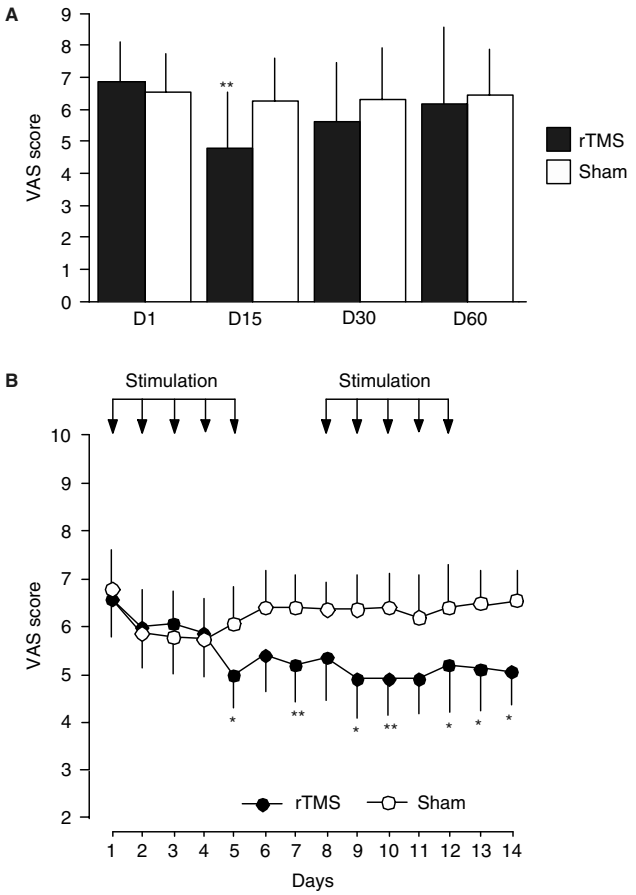

Fig. 1 (**A**) Effects of active rTMS (black columns) and sham stimulation (white columns) of the motor cortex on average pain intensity measured at baseline and 15 (D15), 30 (D30) and 60 (D60) days afer the first stimulation. (**B**) Changes in average pain itensity from D1 to D14 induced by rTMS and sham stimulation. The arrows indicate the stimulation days. $^{*}P < 0.05$; $^{**}P < 0.01$ versus sham stimulation.

days (Fig. 1A). This effect was not maintained on days 30 and 60. An analysis of the patients' pain diaries during the stimulation period showed that average pain intensity was significantly lower in the active rTMS group than in the sham stimulation from day 5 to day 14 (Fig. 1B) ($P < 0.01$).

On day 15, SF-McGill total score and the sensory and affective subscores were significantly lower in the active rTMS group than in the sham-stimulation group (Fig. 2). The difference in affective subscore persisted until D30, whereas that in sensory subscore did not (Fig. 2B and C).

Subjective global pain relief over the last week, as reported by the patients, was significantly greater in the active than in the sham-stimulation group up to day 30 (Fig. 3).

Effects of rTMS on tender points and pressure pain threshold

rTMS had no significant effect on the number of tender points (Table 2). However, rTMS induced a significant increase in pressure pain thresholds measured on D15 for the epicondyle and trochanter contralateral to the stimulation site (Fig. 4). The increase in pain thresholds at these two tender points was correlated with the decrease in average pain intensity on D15 ($r = 0.49$, $P < 0.05$). The effect on pressure pain thresholds was not maintained on days 30 and 60.

Effects of rTMS on quality of life

Active stimulation markedly improved several measures of interference from pain, as assessed by the Brief Pain Inventory (Table 2). BPI-interference scores were similar in the two treatment groups at baseline. Active rTMS induced a significant decrease in pain interference with general activity, sleep and walking until D30 (Table 2). No such effect was observed for sham stimulation. In addition, active rTMS significantly decreased both the total score for the Fibromyalgia Impact Questionnaire (FIQ) and the two subscores related to fatigue and morning tiredness, until D30 (Table 2).

Effects of rTMS on depression and anxiety

Mean depression and anxiety scores (as measured on the HADRS, BDI and HAD scales) were similar in the two treatment groups at baseline and were not significantly affected by active or sham stimulation (Table 2).

Side effects

Minor and transient side effects were reported during the stimulation period only. Nine patients reported headaches: four in the active-stimulation group and five in the sham-stimulation group. These headaches, reported after only 1 of the 10 daily sessions, were mild and transient in all cases. Other side effects included nausea after the fifth session in one patient in the active-treatment group. Two patients reported transient tinnitus and one patient reported mild dizziness after one sham-stimulation session.

Exploratory analysis of predictive factors for the effects of rTMS on pain

We found no correlations between the effects of rTMS on average pain intensity at day 15 and the intensity of baseline pain, the demographic characteristics (age, duration of pain), the baseline scores of anxiety and depression or the number of tender points at baseline.

Discussion

This randomized, double-blind, sham-controlled study, showed that rTMS of the primary motor cortex induced a long-lasting decrease in pain and improved quality of life in patients with fibromyalgia, without affecting mood or anxiety levels. The analgesic effects of rTMS differed for the sensory and affective dimensions of pain. Our data suggest

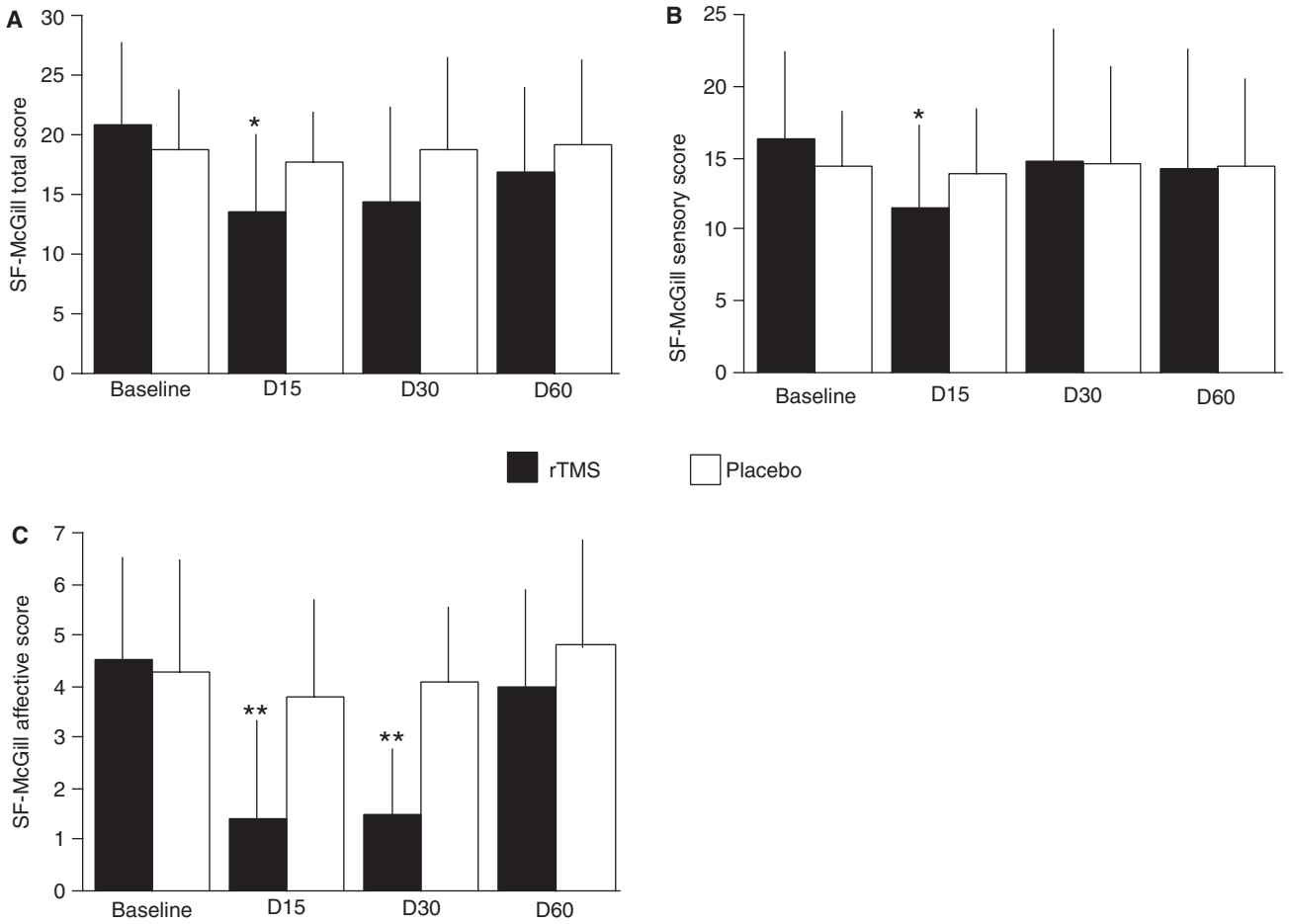

Fig. 2 Effects of active rTMS (black columns) and sham stimulation (white columns) on the total (**A**), sensory (**B**) and affective (**C**) subscores of the McGill Pain Questionnaire at baseline and on days 15, 30 and 60. $^{*}P < 0.05$; $^{**}P < 0.01$ versus sham stimulation.

new therapeutic indications of this technique in chronic pain patients.

Previous studies of rTMS in patients with chronic pain have concerned focal peripheral or central neuropathic pain involving the hand, face or lower limb, contralateral to the stimulation site, and have considered the immediate analgesic effects of a single stimulation session (Migita *et al.*, 1995; Lefaucheur *et al.*, 2001; Rollnik *et al.*, 2002; Canavero *et al.*, 2003; Lefaucheur *et al.*, 2004, 2006; André-Obadia *et al.*, 2006; Fregni *et al.*, 2007). Only one other study considered repeated daily stimulations, over a 5-day period (Khedr *et al.*, 2005). Our data indicate for the first time that rTMS of the motor cortex may also be useful for treating patients with widespread muscle and skeletal pain. These results are consistent with those of a recent study showing that transcranial direct current stimulation of the motor cortex (tDCS) induces long-lasting analgesic effects in fibromyalgia patients (Fregni *et al.*, 2006).

The analgesic effects of repeated daily sessions of rTMS in patient with fibromyalgia were significant only after 5 days of stimulation. These delayed effects are consistent with the observation that pain relief after a single session peaks 2–4 days after rTMS (Lefaucheur *et al.*, 2001) and with recent studies of repeated stimulations using rTMS or tDCS showing maximal effects by the 4th or 5th day of stimulation (Khedr *et al.*, 2005; Fregni *et al.*, 2006). Interestingly, the effects of rTMS in our patients outlasted the stimulation period by up to 3 weeks, which is also in line with prior observations in neuropathic pain using rTMS (Khedr *et al.*, 2005) or in fibromyalgia using tDCS (Fregni *et al.*, 2006). These data suggest that both rTMS and tDCS can induce long-lasting modifications of pain systems in different chronic pain syndromes, without major differences related to the technic of stimulation. In the present study, the analgesic effects were not related to patients sociodemographic or clinical characteristics measured at baseline (i.e. age, pain intensity or duration, anxiety or depression scores, number of tender points). However, it might be of interest to analyse further the relationships between the analgesic effects of rTMS and other patients' characteristics, because in one study the analgesic effects of tDCS were related to the body mass index (Fregni *et al.*, 2006).

The two non-invasive transcranial stimulation techniques may have similar mechanisms of action to chronic motor cortex stimulation with surgically implanted epidural electrodes, which is used in patients with refractory neuropathic pain (Tsubokawa *et al.*, 1991; Katayama *et al.*, 2003; Nguyen *et al.*, 2003; Nuti *et al.*, 2005). Neuroimaging studies (Garcia-Larrea *et al.*, 1999; Peyron *et al.*, 2007) have shown that hemodynamic changes induced in the brain by epidural electrical stimulation are not confined to the motor system, but instead involve a set of cortical (e.g. cingulate, orbitofrontal and prefrontal cortices, thalamus and striatum) and subcortical (e.g. periaqueductal gray matter) areas, involved in pain processing and modulation (Davis, 2000; Peyron *et al.*, 2000; Apkarian *et al.*, 2005; Tracey, 2005). Similar changes in brain activity have been demonstrated after the application of rTMS to the motor cortex (Bohning *et al.*, 2000; Bestmann *et al.*, 2004, 2005; Rounis *et al.*, 2005), suggesting that rTMS can also modulate the activity of brain structures involved in pain perception. In particular, the analgesic effects of rTMS may involve the pain modulation systems of the diencephalon and/or descending from the brainstem to the spinal cord (Lefaucheur, 2006), although other mechanisms such as changes in intracortical inhibitory mechanisms have also been suggested (Lefaucheur *et al.*, 2006*a*). Consistent with these hypotheses, rTMS of the motor cortex, has been shown to reduce experimental pain both in healthy volunteers and in patients with chronic pain (e.g. Kanda *et al.*, 2003; Summers *et al.*, 2004; Tamura *et al.*, 2004; Johnson *et al.*, 2006). In this study, we observed a significant increase in pressure pain thresholds contralateral to the stimulation site, possibly reflecting a direct anti-nociceptive action of rTMS through the activation of descending pain inhibitory controls. This effect was lateralized, but was not organized strictly somatotopically, as it concerned both the upper and lower limbs. These findings are consistent with those of the previous studies showing that the analgesic effects of unilateral rTMS of the motor cortex are not strictly

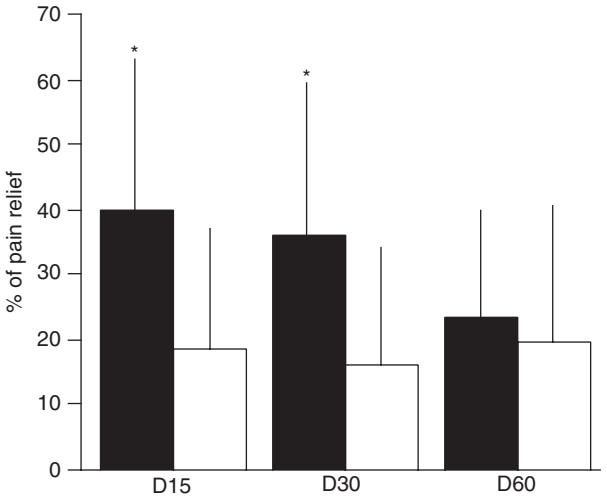

Fig. 3 Percentage of pain relief over the last week reported by the patients on days 15, 30 and 60 in the active rTMS (black column) and sham-stimulation groups (white columns). $^{*}P < 0.05$.

Table 2 Comparison of the effects of active rTMS or sham stimulation on: the number of tender points, the seven items of the Brief Pain Inventory interference (BPI) scores, the total score and the fatigue, rest and stiffness subscales of the Fibromyalgia Impact Questionnaire (FIQ), the Hospital Anxiety and Depression (HAD) scores for anxiety and for depression, Hamilton Depression Rating Scale (HDRS), Beck Depression Inventory (short form) (BDI)

	Baseline rTMS	Sham	15 days rTMS	Sham	30 days rTMS	Sham	60 days rTMS	Sham
Number of tender points (0–18)	16.5 ± 1.5	15.8 ± 2.2	14.0 ± 3.9	16.0 ± 3.2	15.6 ± 4.0	16.2 ± 1.7	15.6 ± 2.6	15.9 ± 2.6
BPI-interference								
General activity (0–10)	7.7 ± 1.5	7.8 ± 1.8	5.6 ± 2.7*	7.1 ± 1.6	5.2 ± 2.5*	6.6 ± 2.0	5.7 ± 2.2	6.8 ± 2.0
Walking (0–10)	6.2 ± 1.6	6.1 ± 2.2	4.7 ± 2.1*	5.8 ± 1.8	4.8 ± 2.2*	5.9 ± 1.7	5.5 ± 3.2	6.5 ± 1.5
Sleep (0–10)	6.8 ± 3.2	6.4 ± 2.2	4.3 ± 2.7*	5.9 ± 2.1	4.6 ± 3.1*	6.0 ± 3.0	5.7 ± 2.3	6.0 ± 3.2
Mood (0–10)	6.6 ± 2.0	5.8 ± 2.6	5.3 ± 2.0	5.1 ± 2.6	4.6 ± 1.8	5.0 ± 2.1	5.0 ± 2.8	5.1 ± 2.1
Normal work (0–10)	6.7 ± 1.7	6.1 ± 1.8	6.0 ± 2.4	6.2 ± 2.2	5.7 ± 2.9	6.1 ± 1.6	5.6 ± 2.9	6.5 ± 2.0
Social relations (0–10)	5.4 ± 2.1	5.4 ± 3.1	4.1 ± 2.8	5.4 ± 2.1	4.3 ± 1.8	4.5 ± 2.2	4.1 ± 2.3	4.7 ± 2.7
Enjoyment of life (0–10)	5.5 ± 2.5	5.2 ± 3.2	4.7 ± 2.4	4.5 ± 2.8	4.6 ± 2.2	4.8 ± 2.3	4.0 ± 2.9	4.6 ± 1.8
FIQ								
Total score (0–100)	63.5 ± 10.8	61.3 ± 11.5	47.4 ± 8.1*	57.8 ± 6.8	48.7 ± 10.4	62.2 ± 8.9	57.2 ± 10.1	63.1 ± 8.8
Fatigue subscale (0–10)	8.4 ± 1.3	8.0 ± 1.5	5.3 ± 2.3*	7.3 ± 1.1	5.3 ± 3.0*	7.0 ± 1.9	6.5 ± 2.5	7.8 ± 2.0
Rest subscale (0–10)	7.8 ± 1.7	8.1 ± 1.4	4.6 ± 2.0*	7.2 ± 2.0	4.4 ± 2.4*	7.6 ± 1.2	6.0 ± 2.4	7.4 ± 2.1
Stiffness subscale (0–10)	7.6 ± 2.2	7.6 ± 1.8	6.5 ± 2.4	7.1 ± 1.5	6.2 ± 2.6	6.5 ± 2.7	6.5 ± 2.3	6.9 ± 2.6
Depression/anxiety								
HDRS (0–52)	9.8 ± 2.3	8.4 ± 3.5	8.3 ± 3.2	7.8 ± 3.5	7.4 ± 4.8	7.1 ± 2.1	7.5 ± 3.6	7.5 ± 4.1
BDI (0–39)	10.2 ± 5.8	8.6 ± 5.2	8.8 ± 5.5	7.5 ± 3.5	8.3 ± 5.4	8.5 ± 4.0	8.5 ± 5.5	7.9 ± 4.7
HAD anxiety score (0–21)	10.3 ± 4.5	10.6 ± 4.5	9.5 ± 4.5	10.4 ± 3.9	8.6 ± 4.2	8.7 ± 3.2	9.4 ± 3.3	8.4 ± 3.4
HAD depression score (0–21)	9.0 ± 4.8	7.8 ± 4.2	8.8 ± 4.1	8.1 ± 3.2	7.8 ± 3.1	8.1 ± 4.4	8.9 ± 4.4	9.1 ± 3.1

Note: Results are expressed as mean ± SD. $^{*}P < 0.05$ versus sham stimulation.

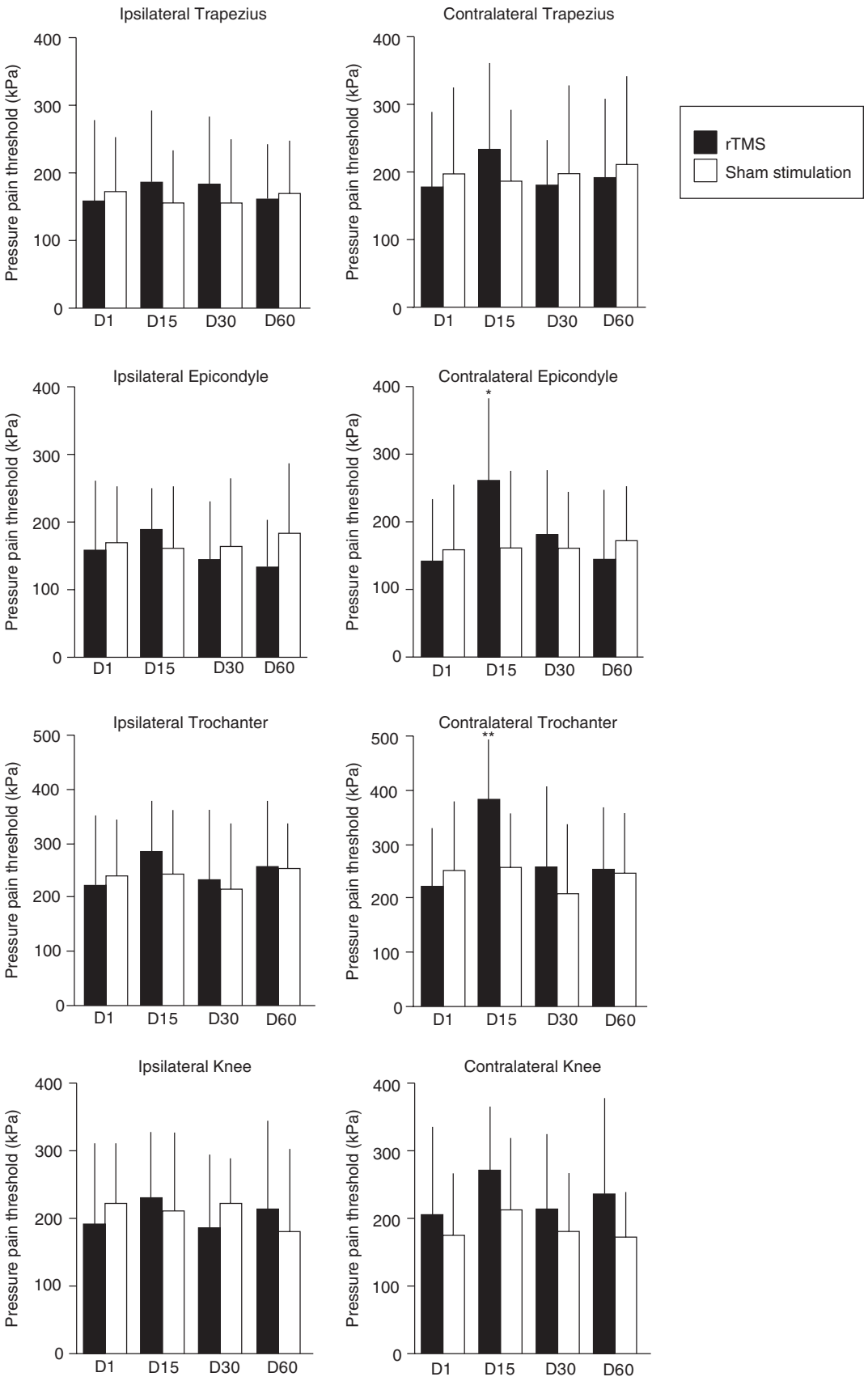

Fig. 4 Effects of active rTMS and sham stimulation on the pressure pain thresholds measured in the ipsi- and contralateral trapezius, epicondyle, trochanter and knee at baseline (D1) and on days 15 (D15), 30 (D30) and 60 (D60) $^{*}P < 0.05$; $^{**}P < 0.01$ versus sham stimulation.

somatotopic (Lefaucheur *et al.*, 2006*b*). The increase in pressure pain threshold at tender points was correlated with a decrease in average pain intensity in our patients. However, this correlation was only moderate and was not maintained over time, suggesting that the clinical analgesic efficacy of rTMS was not exclusively due to its direct anti-nociceptive effects. We also observed long-lasting effects of rTMS on several items related to quality of life, including fatigue, morning tiredness, general activity, walking and sleep. Thus, the effects of rTMS in fibromyalgia patients were not limited to the sensory component of pain but instead corresponded to a more global improvement in chronic pain state. This was also suggested by our striking finding regarding the difference in the duration of rTMS effects on the affective and sensory dimensions of pain, which were not related to changes in mood or anxiety. Thus, the mechanisms of action of rTMS of the motor cortex may differ in the brain structures involved in the affective/emotional component (i.e. the lateral thalamus and the primary and secondary somatosensory cortex) and those preferentially involved in the affective–emotional aspect of pain (i.e. the anterior cingulate and insular cortices) (Davis, 2000; Peyron *et al.*, 2000; Apkarian *et al.*, 2005; Tracey, 2005). However, further clinical and neuroimaging studies are required to confirm the differential effects of rTMS on structures involved in the sensory or affective dimensions of pain in other chronic pain conditions.

The blinding represents one general potential limitation on the interpretation of rTMS effects, because the person who places the active or sham stimulator cannot be blind to the treatment. To overcome this difficulty, the investigator who had to place the simulator in the present study was not involved in the recruitment and evaluation of the patients. We did not confirm the blinding by asking the patients about the treatment they thought they had received, but it is unlikely that they could correctly identify their treatment, since they were all naïve for rTMS and the number and nature of side effects were similar between the active and sham treatments. Furthermore, the possibility, that our results were due solely to unspecific placebo effects of rTMS, seems to be discarded by the observed differential effects of rTMS on the affective and sensory dimensions of pain and the fact that the analgesic effects correlated (at least initially) with an increase in contralateral mechanical pain thresholds.

The present data suggest that rTMS of the primary motor cortex is a potentially effective alternative treatment option in fibromyalgia patients. Fibromyalgia syndrome is a chronic pain condition that is considered very difficult to treat and is associated with severe comorbidity, with a significant impact on quality of life and on the public health system (Robinson *et al.*, 2004; Boonen *et al.*, 2005; Mease, 2005). Recent randomized controlled trials have shown newer anti-depressants (particularly dual reuptake inhibitors), anti-epileptics or dopamine agonists to be beneficial in patients with fibromyalgia (O'Malley *et al.*, 2000; Arnold *et al.*, 2004, 2005; Crofford *et al.*, 2005; Goldenberg *et al.*, 2004). However, the magnitude of the drug-induced analgesic effects generally tend to be lower to those observed in our study, as indicated by their relatively modest effect sizes, ranging from 0.34 for dual reuptake inhibitors to 0.73 for dopamine agonists (Carville *et al.*, in press). Furthermore, tolerance is low for these drugs and compliance with long-term treatment is therefore generally poor. For example, in a recent double-blind placebo-controlled study of the anti-depressant duloxetine, 38% of the patients did not complete the 12-week study, mostly because of side effects (Arnold *et al.*, 2005). In this context, one major advantage of rTMS over pharmacological treatment would be its excellent tolerability. However, further studies are required to define the optimal parameters of stimulation (site, intensity, frequency, etc.). In particular, the effects of right versus left stimulation should be assessed in order to investigate further the lateralization of the effects. Future studies should also confirm that the analgesic effects are sustained over a long period of time with chronic repeated stimulation.

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References

Andre-Obadia N, Peyron R, Mertens P, Mauguiere F, Laurent B, Garcia-Larrea L. Transcranial magnetic stimulation for pain control. Double-blind study of different frequencies against placebo, and correlation with motor cortex stimulation efficacy. Clin Neurophysiol 2006; 117: 1536–44.

Apkarian AV, Bushnell MC, Treede RD, Zubieta JK. Human brain mechanisms of pain perception and regulation in health and disease. Eur J Pain 2005; 9: 463–84.

Arnold LM, Lu Y, Crofford LJ, Wohlreich M, Detke MJ, Iyengar S, et al. A double-blind, multicenter trial comparing duloxetine with placebo in the treatment of fibromyalgia patients with or without major depressive disorder. Arthritis Rheum 2004; 50: 2974–84.

Arnold LM, Rosen A, Pritchett YL, D'Souza DN, Goldstein DJ, Iyengar S, et al. A randomized, double-blind, placebo-controlled trial of duloxetine in the treatment of women with fibromyalgia with or without major depressive disorder. Pain 2005; 119: 5–15.

Beck AT, Rial WY, Rickels K. Short form of depression inventory: cross-validation. Psychol Rep 1974; 34: 1184–6.

Benadhira R, Saba G, Samaan A, Dumortier G, Lipski H, Gastal D, et al. Transcranial magnetic stimulation for refractory depression. Am J Psychiatry 2005; 162: 193.

Bestmann S, Baudewig J, Siebner HR, Rothwell JC, Frahm J. Functional MRI of the immediate impact of transcranial magnetic stimulation on cortical and subcortical motor circuits. Eur J Neurosci 2004; 19: 1950–62.

Bestmann S, Baudewig J, Siebner HR, Rothwell JC, Frahm J. BOLD MRI responses to repetitive TMS over human dorsal premotor cortex. Neuroimage 2005; 28: 22–9.

Bohning DE, Shastri A, Wassermann EM, Ziemann U, Lorberbaum JP, Nahas Z, et al. BOLD-f MRI response to single-pulse transcranial magnetic stimulation (TMS). J Magn Reson Imaging 2000; 11: 569–74.

Boonen A, van den Heuvel R, van Tubergen A, Goossens M, Severens JL, van der Heijde D, et al. Large differences in cost of illness and wellbeing

between patients with fibromyalgia, chronic low back pain, or ankylosing spondylitis. Ann Rheum Dis 2005; 64: 396–402.

Boureau F, Luu M, Doubrere JF. Comparative study of the validity of four French McGill Pain Questionnaire (MPQ) versions. Pain 1992; 50: 59–65.

Burckhardt CS, Clark SR, Bennett RM. The fibromyalgia impact questionnaire: development and validation. J Rheumatol 1991; 18: 728–33.

Canavero S, Bonicalzi V, Dotta M, Vighetti S, Asteggiano G. Low-rate repetitive TMS allays central pain. Neurol Res 2003; 25: 151–2.

Carville SF, Arendt-Nielsen L, Bliddal H, Blotman F, Branco JC, Buskila D, et al. EULAR evidence based recommendations for the management of fibromyalgia syndrome. Ann Rheum Dis 2007 (in press).

Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. Ann Acad Med Singapore 1994; 23: 129–38.

Crofford LJ, Rowbotham MC, Mease PJ, Russell IJ, Dworkin RH, Corbin AE, et al. Pregabalin for the treatment of fibromyalgia syndrome: results of a randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2005; 52: 1264–73.

Davis KD. The neural circuitry of pain as explored with functional MRI. Neurol Res 2000; 22: 313–7.

Fregni F, Freedman S, Pascual-Leone A. Recent advances in the treatment of chronic pain with non-invasive brain stimulation techniques. Lancet Neurol 2007; 6: 188–91.

Fregni F, Gimenes R, Valle AC, Ferreira MJ, Rocha RR, Natalle L, et al. A randomized, sham-controlled, proof of principle study of transcranial direct current stimulation for the treatment of pain in fibromyalgia. Arthritis Rheum 2006; 54: 3988–98.

Fregni F, Simon DK, Wu A, Pascual-Leone A. Non-invasive brain stimulation for Parkinson's disease: a systematic review and meta-analysis of the literature. J Neurol Neurosurg Psychiatry 2005; 76: 1614–23.

Garcia-Larrea L, Peyron R, Mertens P, Gregoire MC, Lavenne F, Le Bars D, et al. Electrical stimulation of motor cortex for pain control: a combined PET-scan and electrophysiological study. Pain 1999; 83: 259–73.

Giesecke T, Gracely RH, Williams DA, Geisser ME, Petzke FW, Clauw DJ. The relationship between depression, clinical pain, and experimental pain in a chronic pain cohort. Arthritis Rheum 2005; 52: 1577–84.

Goldenberg DL, Burckhardt C, Crofford L. Management of fibromyalgia syndrome. JAMA 2004; 292: 2388–95.

Gracely RH, Geisser ME, Giesecke T, Grant MA, Petzke F, Williams DA, et al. Pain catastrophizing and neural responses to pain among persons with fibromyalgia. Brain 2004; 127: 835–43.

Gracely RH, Petzke F, Wolf JM, Clauw DJ. Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia. Arthritis Rheum 2002; 46: 1333–43.

Januel D, Dumortier G, Verdon CM, Stamatiadis L, Saba G, Cabaret W, et al. A double-blind sham controlled study of right prefrontal repetitive transcranial magnetic stimulation (rTMS): therapeutic and cognitive effect in medication free unipolar depression during 4 weeks. Prog Neuropsychopharmacol Biol Psychiatry 2006; 30: 126–30.

Johnson S, Summers J, Pridmore S. Changes to somatosensory detection and pain thresholds following high frequency repetitive TMS of the motor cortex in individuals suffering from chronic pain. Pain 2006; 123: 187–92.

Kanda M, Mima T, Oga T, Matsuhashi M, Toma K, Hara H, et al. Transcranial magnetic stimulation (TMS) of the sensorimotor cortex and medial frontal cortex modifies human pain perception. Clin Neurophysiol 2003; 114: 860–6.

Katayama Y, Yamamoto T, Kobayashi K, Oshima H, Fukaya C. Deep brain and motor cortex stimulation for post-stroke movement disorders and post-stroke pain. Acta Neurochir Suppl 2003; 87: 121–3.

Khedr EM, Kotb H, Kamel NF, Ahmed MA, Sadek R, Rothwell JC. Longlasting antalgic effects of daily sessions of repetitive transcranial magnetic stimulation in central and peripheral neuropathic pain. J Neurol Neurosurg Psychiatry 2005; 76: 833–8.

Kobayashi M, Pascual-Leone A. Transcranial magnetic stimulation in neurology. Lancet Neurol 2003; 2: 145–56.

Kosek E, Ekholm J, Hansson P. Sensory dysfunction in fibromyalgia patients with implications for pathogenic mechanisms. Pain 1996; 68: 375–83.

Kosek E, Hansson P. Modulatory influence on somatosensory perception from vibration and heterotopic noxious conditioning stimulation (HNCS) in fibromyalgia patients and healthy subjects. Pain 1997; 70: 41–51.

Lautenbacher S, Rollman GB. Possible deficiencies of pain modulation in fibromyalgia. Clin J Pain 1997; 13: 189–96.

Lefaucheur JP, Drouot X, Keravel Y, Nguyen JP. Pain relief induced by repetitive transcranial magnetic stimulation of precentral cortex. Neuroreport 2001; 12: 2963–5.

Lefaucheur JP, Drouot X, Menard-Lefaucheur I, Keravel Y, Nguyen JP. Motor cortex rTMS restores defective intracortical inhibition in chronic neuropathic pain. Neurology 2006a; 67: 1568–74.

Lefaucheur JP, Drouot X, Menard-Lefaucheur I, Zerah F, Bendib B, Cesaro P, et al. Neurogenic pain relief by repetitive transcranial magnetic cortical stimulation depends on the origin and the site of pain. J Neurol Neurosurg Psychiatry 2004; 75: 612–6.

Lefaucheur JP, Hatem S, Nineb A, Menard-Lefaucheur I, Wendling S, Keravel Y, et al. Somatotopic organization of the analgesic effects of motor cortex rTMS in neuropathic pain. Neurology 2006b; 67: 1998–2004.

Lefaucheur JP. The use of repetitive transcranial magnetic stimulation (rTMS) in chronic neuropathic pain. Neurophysiol Clin 2006; 36: 117–24.

Londero A, Langguth B, De Ridder D, Bonfils P, Lefaucheur JP. Related repetitive transcranial magnetic stimulation (rTMS): a new therapeutic approach in subjective tinnitus? Neurophysiol Clin 2006; 36: 145–55.

Martin JL, Barbanoj MJ, Schlaepfer TE, Thompson E, Perez V, Kulisevsky J. Repetitive transcranial magnetic stimulation for the treatment of depression. Systematic review and meta-analysis. Br J Psychiatry 2003; 182: 480–91.

Mease P. Fibromyalgia syndrome: review of clinical presentation, pathogenesis, outcome measures, and treatment. J Rheumatol 2005; 75: 6–21.

Melzack R. The McGill pain questionnaire: major properties and scoring methods. Pain 1975; 1: 277–99.

Migita K, Uozumi T, Arita K, Monden S. Transcranial magnetic coil stimulation of motor cortex in patients with central pain. Neurosurgery 1995; 36: 1037–9.

Mountz JM, Bradley LA, Modell JG, Alexander RW, Triana-Alexander M, Aaron LA, et al. Fibromyalgia in women. Abnormalities of regional cerebral blood flow in the thalamus and the caudate nucleus are associated with low pain threshold levels. Arthritis Rheum 1995; 38: 926–38.

NGuyen JP, Lefaucheur JP, Keravel Y. Motor cortex stimulation. In: Simpson B, editor. Electrical stimulation and the relief of pain. Pain research and clinical management. Vol. 15. Amsterdam: Elsevier; 2003. pp. 197–210.

Nuti C, Peyron R, Garcia-Larrea L, Brunon J, Laurent B, Sindou M, et al. Motor cortex stimulation for refractory neuropathic pain: four year outcome and predictors of efficacy. Pain 2005; 118: 43–52.

Okifuji A, Turk DC, Sinclair JD, Starz TW, Marcus DA. A standardized manual tender point survey. I. Development and determination of a threshold point for the identification of positive tender points in fibromyalgia syndrome. J Rheumatol 1997; 24: 377–83.

O'Malley PG, Balden E, Tomkins G, Santoro J, Kroenke K, Jackson JL. Treatment of fibromyalgia with antidepressants: a meta-analysis. J Gen Intern Med 2000; 15: 659–66.

Pascual-Leone A, Rubio B, Pallardo F, Catala MD. Rapid-rate transcranial magnetic stimulation of left dorsolateral prefrontal cortex in drug resistant depression. Lancet 1996; 348: 233–7.

Perrot S, Dumont D, Guillemin F, Pouchot J, Coste J, French Group for Quality of Life Research Quality of life in women with

fibromyalgia syndrome: validation of the QIF, the French version of the fibromyalgia impact questionnaire. J Rheumatol 2003; 30: 1054–9.

Peyron R, Faillenot I, Mertens P, Laurent B, Garcia-Larrea L. Motor cortex stimulation in neuropathic pain. Correlations between analgesic effect and hemodynamic changes in the brain. A PET study. Neuroimage 2007; 34: 310–21.

Peyron R, Laurent B, Garcia-Larrea L. Functional imaging of brain responses to pain. A review and meta-analysis (2000). Neurophysiol Clin 2000; 30: 263–88.

Price DD, Staud R. Neurobiology of fibromyalgia syndrome. J Rheumatol Suppl 2005; 75: 22–8.

Robinson RL, Birnbaum HG, Morley MA, Sisitsky T, Greenberg PE, Wolfe F. Depression and fibromyalgia: treatment and cost when diagnosed separately or concurrently. J Rheumatol 2004; 31: 1621–9.

Rollnik JD, Wustefeld S, Dauper J, Karst M, Fink M, Kossev A, et al. Repetitive transcranial magnetic stimulation for the treatment of chronic pain - a pilot study. Eur Neurol 2002; 48: 6–10.

Rounis E, Lee L, Siebner HR, Rowe JB, Friston KJ, Rothwell JC, et al. Frequency specific changes in regional cerebral blood flow and motor system connectivity following rTMS to the primary motor cortex. Neuroimage 2005; 26: 164–76.

Saba G, Verdon CM, Kalalou K, Rocamora JF, Dumortier G, Benadhira R, et al. Transcranial magnetic stimulation in the treatment of schizophrenic symptoms: a double blind sham controlled study. J Psychiatr Res 2006; 40: 147–52.

Staud R, Cannon RC, Mauderli AP, Robinson ME, Price DD, Vierck CJ, Jr. Temporal summation of pain from mechanical stimulation of muscle tissue in normal controls and subjects with fibromyalgia syndrome. Pain 2003a; 102: 87–95.

Staud R, Robinson ME, Price DD. Isometric exercise has opposite effects on central pain mechanisms in fibromyalgia patients compared to normal controls. Pain 2005; 118: 176–84.

Staud R, Robinson ME, Vierck CJ, Jr,Price DD. Diffuse noxious inhibitory controls (DNIC) attenuate temporal summation of second pain in normal males but not in normal females or fibromyalgia patients. Pain 2003b; 101: 167–74.

Summers J, Johnson S, Pridmore S, Oberoi G. Changes to cold detection and pain thresholds following low and high frequency transcranial magnetic stimulation of the motor cortex. Neurosci Lett 2004; 368: 197–200.

Tamura Y, Okabe S, Ohnishi T, N Saito D, Arai N, Mochio S, et al. Effects of 1-Hz repetitive transcranial magnetic stimulation on acute pain induced by capsaicin. Pain 2004; 107: 107–15.

Tracey I. Nociceptive processing in the human brain. Curr Opin Neurobiol 2005; 15: 478–87.

Tsubokawa T, Katayama Y, Yamamoto T, Hirayama T, Koyama S. Chronic motor cortex stimulation for the treatment of central pain. Acta Neurochir Suppl (Wien) 1991; 52: 137–9.

Wolfe F, Ross K, Anderson J, Russell IJ, Hebert L. The prevalence and characteristics of fibromyalgia in the general population. Arthritis Rheum 1995; 38: 19–28.

Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, et al. The American college of rheumatology 1990 criteria for the classification of fibromyalgia. Report of the multicenter criteria committee. Arthritis Rheum 1990; 33: 160–72.

Wolfe F. The fibromyalgia problem. J Rheumatol 1997; 24: 1247–9.

Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983; 67: 361–70.